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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,377	10/24/2003	James Hunter Boone	TLAB.100292	1630

7590 02/22/2007

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,377	BOONE ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2, 5/04;7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending.

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-27 in the reply filed on November 6, 2006 is acknowledged.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 1-3 are directed to the measurement of fecal lactoferrin in any person , including breast fed infants. In light of evidence provided by US Pat. 6,727,073 which teaches that "fecal lactoferrin found in breast-fed infants is not an effective indicator of an inflammatory intestinal condition, as the presence of lactoferrin from breast milk will lead to false positives." The instantly claimed methods that diagnose inflammatory bowel disease and irritable bowel syndrome in any person, even breast fed infants are not enabled for the claimed invention as the method would result in false positive results.

The Wands factors to be considered:

.the quantity of experimentation necessary: undue due to false positives resulting from fecal lactoferrin originating from sources other than inflammatory neutrophils in breast fed infants and other types of lactoferrin associated diseases and disorders (see Levay et al, 1995, Table 7, page 262);

.the amount of direction or guidance presented: does not provide guidance to exclude

false positive patients;

.the presence or absence of working examples: there are working examples, but determination of lactoferrin in breast fed infants is not described/claimed in such a way as to differentiate between various inflammatory bowel diseases;

.the nature of the invention: unpredictable in light of multiple sources of fecal lactoferrin can cause false positives in a patient;

.the state of the prior art: still developing with respect to which markers clearly determine/distinguish various forms of inflammatory bowel disease (see Bossuyt (2006, who shows variability in the presentation of markers in patients with inflammatory bowel disease, see entire article, where control patients present with autoantibodies to neutrophic antigens (see Table 3, page 173; as well as ASCA healthy controls (see Table 4, page 175); Glaffer 1991 teaches IgA anti-ASCA antibodies are increased while IgG antibodies to ASCA are not; Oshitani et al (2001) further show only IgG4 is increased and not IgG1, G2 and G3 are not increased in inflammatory bowel disease.

.the relative skill of those in the art: high (immunoassay methods of determining an analyte);

.the predictability or unpredictability of the art: unpredictable in light of false positives due to breast fed infants would evidence elevated fecal lactoferrin levels and Bossuyt showing negative control patients to present with autoantibodies to neutrophil antigens and Saccharomyces cerevisiae (see page 173, Table 3 and page 175, Table 4);

.breadth of the claims: broad.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

5. The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-27 provides for the use of lactoferrin (see claim 1 "is present"; claims 2-3, 6-7, 23 "is used"; claims 4-6 "may be"; 8-10: "are measured" , "is measured" etc.), but, since the claims do not set forth any active, positive steps delimiting how this use is actually practiced.

7. Claims 17-19 and 20-22 recite method steps of adding antigens to the sample of claims 11 and 1, but the methods of detecting anti-Saccharomyces cerevisiae antibodies and anti-neutrophil cytoplasmic antibodies are optionally set forth in claims 1 and 11 by the recitation **"if so"**. The methods of claims 17-19 and 20-22 are optional methods steps to only be carried out when the lactoferrin level in the patient sample of claim 1 is positive, the samples of claims 17-22 are not defined to be positive, and therefore set forth a combination of claim limitations that

are only optionally carried out. The recitation of additional optional methods steps does not further limit the optional method of claims 1 and 11. The recitation of "further comprises" additional optional methods steps, does not set forth positively recited methods steps for the claimed methods.

8. Claims 13-14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13-16 create a readable sample by contacting the treated sample with enzyme-linked polyclonal antibodies, but how the antibodies create the readable sample is not clearly nor distinctly claimed, in light of the critical and essential binding specificity of the polyclonal antibodies is not claimed. See In re Mayhew.

9. Claims 13-14, 17-18 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are:

10. the polyvalent antibodies to human immunoglobulin labeled with horseradish peroxidase added to a diluted fecal sample that is readable at 450 nm (claims 13-14 and 21-23).

11. a substrate must be added to the fecal samples in order for the enzyme in the enzyme-linked immunoglobulin/antibody complex to generate an emission spectra which is then read. No substrates for the recite enzymes of claims 13-14, 17-18 and 21-23) have been added to the samples.

12. The polyclonal antibodies of claims 21-23 do not comprise an enzyme and therefore what is readable in the treated sample is unclear and incomplete. The claims are incomplete by

omitting an essential enzyme/substrate for producing a readable sample. Additionally, claim 22 determines an optical density at 450 nm, but no reagents or components in the fecal sample are positively recited as comprising an emission spectra of 450 nm in the diluted fecal sample. What components in the fecal sample are readable at 450 nm? An essential element is missing form the claim that would be readable at 450 nm. See In re Mayhew.

13. Claims 13-14, 18-19 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: forming antigen/antibody complexes specific to lactoferrin, Saccharomyces cerevisiae antigens and neutrophil cytoplasmic antigens and removing any non-specific human immunoglobulin not contained in the specific antigen/antibody complexes, adding anti-human immunoglobulin antibodies labeled with an enzyme; adding enzyme substrate to produce a readable sample. The methods as now claimed detect any human immunoglobulin that is readable and fecal samples are known to contain a plurality of immunoglobulins that are not directed to lactoferrin, Saccharomyces cerevisiae antigens and neutrophil cytoplasmic antigens . The methods as now claimed are not directed to specifically detected only those antibodies or human immunoglobulins that are antigen specific for the antigens recited in claim 1.

14. Claims 15-16 recite the limitation "purified lactoferrin" in dependence upon claims 1, 11-14. Claims 1, 11-14 do not recite any purification steps, and the only source of lactoferrin

recited in the claims is the fecal sample of claim 1, which may or may not contain lactoferrin. There is insufficient antecedent basis for this limitation in the claim

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1,8-12, 13, 15 and 24-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerrant et al (US Pat. 5,124,252).

Instant claim 1 and 24: Guerrant et al disclose the instantly claimed invention directed to a method, the method comprising the steps of:

17. obtaining a fecal sample from a person (see abstract);

18. determining whether lactoferrin is present in the sample (three additional control specimens tested on 7 different occasions were all negative (see col. 3, lines 63-64).

Instant claim 8-10: wherein the presence of lactoferrin is measured by ELISA (see col. 4, lines 23-60, especially lines 30-31).

Instant claim 11:further comprising diluting the sample (see col. 2, lines 38-42 "mixed with an equal amount of 0.1% Triton-X".)

Instant claim 12: further comprising contacting the sample with immobilized polyclonal antibodies "Bacto-latex beads were coated with rabbit anti-human lactoferrin" and this latex bead suspension was added to "22 fecal specimens (see col. 4, lines 1-11), the endogenous lactoferrin being released by the leukocytes (see col. 4, lines 12-16 "children with diarrhea in the northeast of Brazil").

Instant claim 13: further comprising contacting said treated sample with enzyme liked polyclonal antibodies to create a readable sample (see col. 4, lines 42-44 "peroxidase conjugation", read both visually and spectrophotometically (see col. 4, line 49 and claim 4). While the reference is silent with respect to whether the rabbit antibodies are polyclonal or monoclonal antibodies, it is clear that the reference does not discuss nor describe the production of hybridoma and monoclonal production, therefore the antibodies are conventional rabbit sera that comprise polyclonal antibodies.

Instant claim 15: further comprising generating a purified lactoferrin standard curve (see col. 4, lines 29-32, varying concentrations of lactoferrin were coated in the wells). The sensitivity of the assay was 0.001 ug/ml or less lactoferrin (see claim 4). Guerrant et al (US Pat. 5,124,252) anticipates the instantly claimed invention that does not require the claimed method to measure anything more than endogenous lactoferrin when the sample when the lactoferrin determination is considered negative in light of all the claims reciting the phrase "if so", which makes the following methods steps optional. Guerrant et al (US Pat. 5,124,252) anticipates the instantly claimed invention as now claimed.

19. Claims 1-3,11-12 and 24-26, 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Fine et al (AJG, 1998).

Instant claim 1-3 and 24-27: Fine et al disclose the instantly claimed invention directed to a method, the method comprising the steps of:

20. obtaining a fecal sample from a person (see page 1301, col. 2, first two paragraphs);

21. determining whether lactoferrin is present in the sample (see page 1302, Table 1 "Diagnoses in 92 Patients with a negative fecal lactoferrin Test", one patients test changed levels upon repeating the lactoferrin determination (see page 1302, Table 1, bottom of ledger narrative). The lactoferrin data was used to distinguish the patients that have inflammatory bowl disease or syndrome from those patients that have another bowl condition (see page 1302, Table 1).

Instant claim 11:further comprising diluting the sample (see page 1301, col. 2, paragraph 3).

Instant claim 12: further comprising contacting the sample with immobilized polyclonal antibodies latex beads were coated with rabbit anti-human lactoferrin, the endogenous lactoferrin is detected with the immobilized polyclonal antibodies. While the reference is silent with respect to whether the rabbit antibodies are polyclonal or monoclonal antibodies, it is clear that the reference does not discuss nor describe the production of hybridoma cell lines and monoclonal antibody production, therefore the antibodies are present in conventional rabbit sera that comprise polyclonal antibodies.

Fine et al anticipates the instantly claimed invention that does not require the claimed method to measure anything more than endogenous lactoferrin when the sample when the lactoferrin determination is considered negative in light of all the claims reciting the phrase "if

so", which makes the following methods steps optional. Fine et al anticipates the instantly claimed invention as now claimed.

22. Claims 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Martins et al (1995). Martins et al disclose a method that comprises the step of :

Obtaining a whole blood, saliva, sputum (mucosal secretion sample) and gingival swabs (bodily fluid) from a patient (see abstract);

Determining whether lactoferrin is present in the sample (see abstract, negative for lactoferrin as an inflammatory marker in 7 individuals with healthy gums and teeth ; 4 edentulous patients were negative (see Figure 1 and 2, page 764). Martins et al anticipates the instantly claimed invention as now claimed.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 1-10, 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nielsen et al (2000) in view of Targan et al (1995) and Fine (PG-Pub 2001/0036639A1, filing date March 2, 2001).

Nielson et al describe biological activity markers of Inflammatory Bowel Disease (see title, page 359), wherein the markers include fecal lactoferrin (see page 360, col. 2, paragraph 1),

and autoantibodies known as ANCA and ASCA (see page 361, col. 1-2). Nielson et al teach the methods step of :

Obtaining a fecal sample from a patient and determining the presence of fecal lactoferrin (see page 360, col. 2, paragraph 1) in order to provide for both sensitive and bowel-specific markers of disease and further determining the presence or absence of ASCA and ANCA in the patient (see page 361, col. 1-2).

Nielson et al teach the importance of assessing disease activity in inflammatory bowel disease (IBD), to include ulcerative colitis and Crohn's disease based upon clinical parameters and various biological disease markers (see page 359, col. 1, abstract, first sentence), but differs from the instantly claimed invention by failing to determine ANCA and ASCA in the fecal sample.

Targan et al (1995) teach ANCA antibodies are presenting mucosal lesions of the bowel (whole abstract; and page 3266, col. 2, paragraph 1) in ulcerative colitis patients (non-serum samples, see table II, page 3265; p3264, Figure 1, Table 1; diluted 1:2 (see page 3264, Results section, first paragraph) in an analogous art for the purpose of quantitatively (see Table 1, page 3264, col. 5) defining pANCA production is a consequence of a mucosal immune response associated with ulcerative colitis (full last sentence of abstract; Fig. 1, p 3264). Fine et al (20010036639) teach a method of measuring fecal antibodies directed to Saccharomyces cervesiae (ASCA) (see claims 1, 19-21 and 43; [0054]) in an analogous art for the purpose of determining the presence of antibodies associated with diseases or disorders of the bowel, to include diagnosis of irritable bowel syndrome (see page 3, [0020] and [0015; 0018, entire paragraph, as well as second half of paragraph. "diarrhea"]).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to measure fecal lactoferrin, ANCA and ASCA in a patient fecal sample because Nielson et al teach biological markers associated with inflammatory bowel disease, and teach fecal lactoferrin, as well as ANCA and ASCA to provide insight into disease activity associated with inflammatory bowel disease (see Nielsen et al, abstract, page 360, col. 2, p.1 and page 361, col. 1-2) and Targan et al and Fine et al teach the presence of ANCA and ASCA markers, respectively, are present in fecal/mucosal bowel samples and could be measured in the patient fecal sample along with the fecal lactoferrin determination. The person of ordinary skill in the art would have been motivated to determine fecal lactoferrin, along with fecal ANCA and ASCA markers because Nielsen et al teach that the lactoferrin is a measure of active bowel disease and measurement of ANCA and ASCA provide for differential diagnosis of the patient's type of inflammatory bowel disease (see Nielsen et al, page 361, col. 2, paragraph 3).

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of determining the presence or absence of inflammatory bowel disease (see page 360, col. 1, p. 1) by determining the fecal lactoferrin test, a marker for active bowel inflammatory disease, as taught by Nielsen et al, and if positive, further determining the presence and amount of ANCA and ASCA antibodies in the fecal sample because Nielsen et al teach that the "combined measurement of pANCA and ASCA may be used advantageously in the sub-classification of IBD patients with indeterminate colitis. Both antibody specificities are measured by traditional quantitative solid phase immunosorbent assays, and they are highly specific (>90%) for both UC and CD with disease sensitivity around 50% in both cases (see Nielsen et al, page 361, col. 2, paragraph 3)."

Nielsen et al in view of Targen et al and Fine et al obviate the instantly claimed invention as now claimed.

Conclusion

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US005552292A is cited to show fecal lactoferrin as a marker for colorectal cancer (abstract).
26. Kayazawa et al (Feb. 2002) is cited to show measurement of lactoferrin in whole gut lavage fluid as a marker for disease activity in inflammatory bowel disease.
27. Peen et al (1993) is cited to show anti-lactoferrin antibodies and other types of ANCA in ulcerative colitis, PSC and Crohn's diseases.
28. Saitoh et al (page 3518) is cited to show fecal lactoferrin to be a useful marker for the presence of minimal intestinal inflammatorion in UC and CD, and elevated in almost all patients with active UC, indicating that bleeding and mucosal neutrophil infiltration are common features of all patients with UC.
29. Tribble et al (2001) is cited to show the measurement of stool lactoferrin as a marker for intestinal inflammation (see abstract and page 463, col. 2).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vgp
January 9, 2007

MARK NAVARRO
PRIMARY EXAMINER